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Is It Worth It?: A Review of the Current Diagnostic Tools and Understandings of Athletes Suffering with CTE

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Is it worth it?

A review of the current diagnostic tools and understandings of athletes suffering with CTE

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I. Abstract

II. Introduction

- Adam, Octavian. “Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan.” Neurology. 85 (2015), 219-227.

- Barrio, Jorge R. “In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging.” Proceedings of the National Academy of Sciences of the United State of America. (2015), 2039-2047.

- Lipton, Michael L. “Soccer heading is associated with white matter microstructural and cognitive abnormalities.” Radiology. 268 (2013), 850–857.

- McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

- The New York Times. “The N.F.L.’s tragic C.T.E. roll call.” http://www.nytimes.com/interactive/2016/02/03/sports/football/nfl-brain-disease-cte-concussions.html

- Rubenstein, Richard. “A novel, ultrasensitive assay for tau: Potential for assessing traumatic brain injury in tissues and biofluids.” Journal of Neurotrauma. 32 (2015), 342–352.

1. Thesis: Imaging techniques combined with established autopsy findings and patient history will have a profoundly positive effect in the development of an accurate diagnosis for CTE.

III. CTE

1. What is CTE?
    - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

    - Stern, Robert A. “Clinical presentation of chronic traumatic encephalopathy.” American Academy of Neurology. 81 (2013), 1122-1129.

        - Both sources were used as background information and used to define CTE

    a. Discovery of CTE
        - McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.
            - McKee Stages of CTE I-IV

        - Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

    b. Neurodegenerative disease
        - Gardner, Raquel C. “Epidemiology of mild traumatic brain injury and neurodegenerative disease.” Molecular and Cell Neuroscience. 66 (2015), 75-80.

        - McKee, Ann C. “The neuropathology of chronic traumatic encephalopathy.” Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

    c. Discovery of Tau in CTE

- Corsellis, J. “The aftermath of boxing.” Psychological Medicine. 3 (1973), 270-303.

- Johnson, Victoria E. “Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans.” Brain Pathology (Zurich, Switzerland). 22 (2012), 142–149.

- McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

- Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

- Stern, Robert A. “Clinical presentation of chronic traumatic encephalopathy.” American Academy of Neurology. 81 (2013), 1122-1129.

- Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

d. Tauopathy
   - Williams, D.R. “Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau.” Internal Medicine Journal. 36 (2006), 652-660

   i. Tau protein
   - Cook, Casey. “Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance.” Human Molecular Genetics. 23 (2014), 104-116.

   - Lucke-Wold, Brandon. “Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development.” Journal of Neurotrauma. 31(2014), 1129–1138.

   - McKee, Ann C. “The neuropathology of chronic traumatic encephalopathy.” Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

   - Rubenstein, Richard. “A novel, ultrasensitive assay for tau: Potential for assessing traumatic brain injury in tissues and biofluids.” Journal of Neurotrauma. 32 (2015), 342–352.

e. Other potentially associated proteins and risks for neurodegenerative disease
   1. TDP-43
      - Costanza, Alessandra. “Review: Contact sport-related chronic traumatic encephalopathy in the elderly: Clinical expression and structural substrates.” Neuropathology and Applied Neurobiology. 37 (2011): 570–584.

      - Lucke-Wold, Brandon. “Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development.” Journal of Neurotrauma. 31(2014), 1129–1138.

- McKee, Ann C. “TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy.” Journal of Neuropathology and Experimental Neurology. 69 (2010), 918-929.

- Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

2. β-Amyloid
   - Costanza, Alessandra. “Review: Contact sport-related chronic traumatic encephalopathy in the elderly: Clinical expression and structural substrates.” Neuropathology and Applied Neurobiology. 37 (2011): 570–584.

   - McKee, Ann C. “TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy.” Journal of Neuropathology and Experimental Neurology. 69 (2010), 918-929.

   - Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

   - Johnson, Victoria E. “Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans.” Brain Pathology (Zurich, Switzerland). 22 (2012), 142–149.

3. α-Synuclein
   - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

   - Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

   - Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

f. Prion theory
   - Prusiner, Stanley B. “Biology and genetics of prions causing neurodegeneration.” Annual Review of Genetics. 47 (2013), 601–623.
     - Prusiner paper was a complete coverage of his work and current knowledge of prion development.

2. Current theory of causation
   - Gardner, Raquel C. “Epidemiology of mild traumatic brain injury and neurodegenerative disease.” Molecular and Cell Neuroscience. 66 (2015), 75-80.

   - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

3. When does CTE develop?
   a. Later stages in life
      - Costanza, Alessandra. “Review: Contact sport-related chronic traumatic encephalopathy in the elderly: Clinical expression and structural substrates.” Neuropathology and Applied Neurobiology. 37 (2011): 570–584.

- McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

- Mitsis, E. M. “Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: Studies of a retired NFL player and of a man with FTD and a severe head injury.” Translational Psychiatry. 4 (2014), 1-8.

b. General age range
   - Mez, Jesse. “Chronic traumatic encephalopathy: Where are we and where are we going?” Current Neurology and Neuroscience Reports. 13 (2013), 1-23.

4. Details of injury and how CTE is caused
   a. Concussive vs. sub-concussive injury
      - Costanza, Alessandra. “Review: Contact sport-related chronic traumatic encephalopathy in the elderly: Clinical expression and structural substrates.” Neuropathology and Applied Neurobiology. 37 (2011): 570–584.

      - Gardner, Raquel C. “Epidemiology of mild traumatic brain injury and neurodegenerative disease.” Molecular and Cell Neuroscience. 66 (2015), 75-80.

   b. Single vs. multiple injuries
      - Adam, Octavian. “Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan.” Neurology. 85 (2015), 219-227.

      - Gardner, Raquel C. “Epidemiology of mild traumatic brain injury and neurodegenerative disease.” Molecular and Cell Neuroscience. 66 (2015), 75-80.

      - Johnson, Victoria E. “Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans.” Brain Pathology (Zurich, Switzerland). 22 (2012), 142–149.

      - McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

      - Mez, Jesse. “Chronic traumatic encephalopathy: Where are we and where are we going?” Current Neurology and Neuroscience Reports. 13 (2013), 1-23.

      - Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

      - Rubenstein, Richard. “A novel, ultrasensitive assay for tau: Potential for assessing traumatic brain injury in tissues and biofluids.” Journal of Neurotrauma. 32 (2015), 342–352.

   c. Force trauma data
      i. Murine models
         - Goldstein, Lee E. “Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model.” Science Translational Medicine. 4 (2012), 1-14.
            - Figure 2 data regarding kinematics of blast-induced trauma to mice with intracranial pressures.

- Rubenstein, Richard. “A novel, ultrasensitive assay for tau: Potential for assessing traumatic brain injury in tissues and biofluids.” Journal of Neurotrauma. 32 (2015), 342–352.
    - Figure 1 was adapted from Rubenstein et al by comparing murine model p and t tau levels to humans with severe traumatic brain injury.

ii. Human accelerometer data

- Rowson, Steven. “Rotational head kinematics in football impacts: an injury risk function for concussion.” Annals of Biomedical Engineering. 40 (2012), 1–13.
    - Table 1 adapted from planes of rotation observed with concussive and subconcussive events.
    - Figure 3 displays data observed by Rowson, risk assessment for concussion with observed accelerations.

d. Who it affects and associated risks

- Lucke-Wold, Brandon. “Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development.” Journal of Neurotrauma. 31(2014), 1129–1138.

- McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

i. Athletes

- Costanza, Alessandra. “Review: Contact sport-related chronic traumatic encephalopathy in the elderly: Clinical expression and structural substrates.” Neuropathology and Applied Neurobiology. 37 (2011): 570–584.

- Lipton, Michael L. “Soccer heading is associated with white matter microstructural and cognitive abnormalities.” Radiology. 268 (2013), 850–857.

- McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

ii. Military personnel

- Adam, Octavian. “Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan.” Neurology. 85 (2015), 219-227.

- Goldstein, Lee. “Chronic traumatic encephalopathy in blast-exposed military veterans and blast neurotrauma mouse model.” Science Translational Medicine. 4 (2012), 1-14.

iii. Victims of Abuse

- Dams-O’Connor, Kristen. “Screening for traumatic brain injury: Findings and public health implications.” The Journal of Head Trauma Rehabilitation. 29 (2014), 479-489.

- McKee, Ann C. “The neuropathology of chronic traumatic encephalopathy.” Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

5. Other contributory factors to CTE development
   a. Age
      - Maroon, Joseph C. “Chronic traumatic encephalopathy in contact sports: A systematic review of all reported pathological cases.” PloS One. 10 (2015), 1-16.
      - Mez, Jesse. “Chronic traumatic encephalopathy: Where are we and where are we going?” Current Neurology and Neuroscience Reports. 13 (2013), 1-23.
      - Turner, Ryan C. “Modeling chronic traumatic encephalopathy: The way forward for future discovery.” Frontiers in Neurology. 6 (2015), 1-18.

   b. Sex
      - Bramlett, Helen M. “Neuropathological protection after traumatic brain injury in intact female rats versus males or ovariectomized females.” Journal of Neurotrauma. 18 (2001), 891-900.
      - Kovacs, Elizabeth J. “Estrogen regulation of immune responses after injury.” Molecular and Cellular Endocrinology 193 (2002): 129–135.
      - Mez, Jesse. “Chronic traumatic encephalopathy: Where are we and where are we going?” Current Neurology and Neuroscience Reports. 13 (2013), 1-23.

6. Parts of the brain affected by CTE
   a. Multiple gross anatomical regions of the brain
      - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.
        - Figure 4 displays tau staining as it is observed in stages I-IV.
      - Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.
      - Sundman, Mark. “Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: Implications for CTE.” Frontier Neuroscience. 9 (2015), 1-15.
        - Table 2 summarizes all four stages of CTE development as created by McKee et al. Gross, tau, other proteins and clinical symptoms included.

   i. Vascular changes perceived in mTBI
      - Doshi, Hardik. “Cerebral hemodynamic changes of mild traumatic brain injury at the acute stage.” PloS One. 10 (2015), 1-18.

   b. Neural cells
      - Lucke-Wold, Brandon. “Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development.” Journal of Neurotrauma. 31(2014), 1129–1138.

- McKee, Ann C. “The neuropathology of chronic traumatic encephalopathy.” Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

- Gao, Xiang. “Mild traumatic brain injury results in extensive neuronal degeneration in the cerebral cortex.” Journal of Neuropathology and Experimental Neurology. 70 (2011): 183–191.

- Goldstein, Lee. “Chronic traumatic encephalopathy in blast-exposed military veterans and blast neurotrauma mouse model.” Science Translational Medicine. 4 (2012), 1-14.

c. Behavioral and cognitive changes
   - Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

   - McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

   - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

   - Stern, Robert A. “Clinical presentation of chronic traumatic encephalopathy.” American Academy of Neurology. 81 (2013), 1122-1129.

     - Table 3 displayed differences observed in clinical presentation of CTE behavior prior to death.

   - Sundman, Mark. “Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: Implications for CTE.” Frontier Neuroscience. 9 (2015), 1-15.

     - Table 2 summarizes all four stages of CTE development as created by McKee et al. Gross, tau, other proteins and clinical symptoms included.

d. Potential changes in motor function
   - Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

   - McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

   - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

7. Factors that could interfere with CTE diagnosis
   - Maroon, Joseph C. “Chronic traumatic encephalopathy in contact sports: A systematic review of all reported pathological cases.” PloS One. 10 (2015), 1-16.

- McKee, Ann C. “The neuropathology of chronic traumatic encephalopathy.” Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

- Doshi, Hardik. “Cerebral hemodynamic changes of mild traumatic brain injury at the acute stage.” PloS One. 10 (2015), 1-18.

8. Assessment tools for CTE development
    a. Past and current confirmed CTE diagnosis
        - McKee, Ann C. “Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury.” Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.
        - Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

        - Saing, Tommy. “Frontal cortex neuropathology in dementia pugilistica.” Journal of Neurotrauma. 29 (2012), 1054–1070.

    b. Recent contributions to current practices in development
        i. Blood serum and cerebrospinal fluid assays
        - Rubenstein, Richard. “A novel, ultrasensitive assay for tau: Potential for assessing traumatic brain injury in tissues and biofluids.” Journal of Neurotrauma. 32 (2015), 342–352.
            - Figure 1 was adapted from Rubenstein et al by comparing murine model p and t tau levels to humans with severe traumatic brain injury.

        ii. PET scanning and biomarkers
            a. Biomarkers
        - Dani, Melani. “Imaging biomarkers in tauopathies.” Parkinsonism and Related Disorders. 22 (2016), S26-S28.

        - Dickstein, D. L. “Cerebral [18 F]T807/AV1451 retention pattern in clinically probable CTE resembles pathognomonic distribution of CTE tauopathy.” Translational Psychiatry. 6 (2016), 1-8.

        - Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

        - Liu, Jie. “High-yield, automated radiosynthesis of 2-(1-{6- [(2-[18F] fluoroethyl) (methyl) amino]-2-naphthyl} ethylidene) malononitrile, ([18 F] FDDNP) ready for animal or human administration.” Molecular Imaging and Biology. 9 (2007), 6-16.

        - Mitsis, E. M. “Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: Studies of a retired NFL player and of a man with FTD and a severe head injury.” Translational Psychiatry. 4 (2014), 1-8.

        - Zimmer, E.R. “Developments in tau PET imaging.” The Canadian Journal of Neurosciences. 41 (2014), 547-553.

            - Table 4 adapted from data observed by Dani et al, Liu et al and Zimmer et al on biomarker binding affinity.

            b. PET scanning in a living person

- Barrio, Jorge R. “In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging.” Proceedings of the National Academy of Sciences of the United State of America. (2015), 2039-2047.
    - [F-18] FDDNP PET signal patterns for stages T1-T4, core regions were determined to be the amygdala and dorsal midbrain which consistently presented in the football player group indicated by stronger signals (Barrio et al, 2015). Overlap between brain locations found in Alzheimer’s disease (AD) group and mTBI group were distinguished by a stronger signal in the mTBI grouping.

- Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

- Liu, Jie. “High-yield, automated radiosynthesis of 2-(1-{6- [(2-[18F] fluoroethyl) (methyl) amino]-2-naphthyl} ethylidene) malononitrile, ([18 F] FDDNP) ready for animal or human administration.” Molecular Imaging and Biology. 9 (2007), 6-16.

- McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.
    - Figure 4 displays tau staining as it is observed in stages I-IV.

iii. DTI scanning

- Adam, Octavian. “Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan.” Neurology. 85 (2015), 219-227.
    - Figure 6 displayed slight changes in fractional anisotropy graph and one image of a brain with white matter structural changes vs. control.

- Lipton, Michael L. “Soccer heading is associated with white matter microstructural and cognitive abnormalities.” Radiology. 268 (2013), 850–857.

- Mori, Susumu. “Principles of diffusion tensor imaging and its applications to basic neuroscience research.” Neuron. 51 (2006), 527–539.

9. How imaging techniques will provide a more accurate diagnosis of CTE
    - Barrio, Jorge R. “In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging.” Proceedings of the National Academy of Sciences of the United State of America. (2015), 2039-2047.

    - Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

    - Mez, Jesse. “Chronic traumatic encephalopathy: Where are we and where are we going?” Current Neurology and Neuroscience Reports. 13 (2013), 1-23.

10. Potential treatment for CTE
    - Feng, H.L. “Rapid report: Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model.” Neuroscience. 155 (2008), 567-572.

    - Jope, Richard S. “Lithium and GSK-3: One inhibitor, two inhibitory actions, multiple outcomes.” TRENDS in Pharmacological Sciences. 24 (2003), 441-443.

- Leeds, Peter R. “A new avenue for lithium: Intervention in traumatic brain injury.” American Chemical Society Chemical Neuroscience. 5 (2014), 422-433.

- Lucke-Wold, Brandon. “Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development.” Journal of Neurotrauma. 31(2014), 1129–1138.

IV. Past and current opinions on CTE in sports

1. Societal views

a. Acceptance of facts

- Anderson, Eric. “Examining media contestation of masculinity and head trauma in the national football league.” Men and Masculinities. 15 (2012), 152-173.

- Fainaru, Steven. “NFL acknowledges, for the first time, link between football, brain disease.” http://www.espn.com/espn/otl/story/_/id/14972296/top-nfl-official-acknowledges-link-football-related-head-trauma-cte-first.

- Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

- Seichepine, Daniel R. “Profile of self-reported problems with executive functioning of college and professional football players.” Journal of Neurotrauma. 30 (2013), 1299-1304.

- Youtube, FOX Sports. NFL on FOX: Concussion Discussion. https://www.youtube.com/watch?v=s0Vsx1iOJ6k

a. Denial of facts

- Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

- Goldberg, Daniel S. “Mild traumatic brain injury, the national football league, and the manufacture of doubt: An ethical, legal, and historical analysis.” The Journal of Legal Medicine. 34 (2013), 157-191.

- Kroshus, Emily. “Pressure on sports medicine clinicians to prematurely return collegiate athletes to play after concussion.” Journal of Athletic Training. 50 (2015), 944–951.

- Robbins, Clifford A. “Self-reported concussion history: impact of providing a definition of concussion.” Open Access Journal of Sports Medicine. 5 (2014), 99-103.

- Youtube, Charlie Rose. Ray Lewis: “I’m Not Worried About Concussions’ in the NFL (Oct. 20, 2015) | Charlie Rose. https://www.youtube.com/watch?v=KbtkcQ5umPA

- Youtube, FOX Sports. NFL on FOX: Concussion Discussion. https://www.youtube.com/watch?v=s0Vsx1iOJ6k

2. Athlete complaints

a. Litigation

- In Re National Football League Players' concussion Injury Litigation, (Dist. Court 2015). Westlaw search.

- In Re National Hockey League Players' concussion Injury Litigation, (Dist. Court 2016). Westlaw search.

b. Quality of life with CTE

- Youtube, AXS TV Fights. Living With CTE: Inside MMA Catches Up With "Big Daddy" Gary Goodridge. Accessed September 25, 2016. https://www.youtube.com/watch?v=S5OUt53-6YM.

- Youtube. "CTE." Accessed September 25, 2016. https://www.youtube.com/watch?v=4ZxIUz4sc0U.

- McKee, Ann C. "Chronic traumatic encephalopathy in athletes: Progressive tauopathy following repetitive head injury." Journal of Neuropathology and Experimental Neurology. 68 (2009), 709-735.

- Omalu, Bennet. "Chronic Traumatic Encephalopathy in a national football league player." Neurosurgery. 57 (2005), 128-134.

V. Potential solutions for CTE prevention

1. Updating equipment (currently in development)

a. Shock absorbing helmets (VICIS Zero 1 helmet)

- Browd, Samuel R. "Protective helmets with non-linearly deforming elements." US20160255900 A1, filed November 5, 2014, and issued September 8, 2016. http://www.google.com/patents/US20160255900.

- vicis.co/ Corporate and product information site.

2. Side line test and return-to-play instructions

- Kroshus, Emily. "Understanding concussion reporting using a model based on the theory of planned behavior." Journal of Adolescent Health. 54 (2014), 269-274.

- Leong, Danielle F. "The King-Devick test for sideline concussion screening in collegiate football." Journal of Optometry. 8 (2015), 131–139.

- Williams, Richelle M. "Concussion recovery time among high school and collegiate athletes: A systematic review and meta-analysis." Sports Medicine (Auckland, N.Z.). 45 (2015), 893–903.

3. Putting an age limit on certain full-contact sports

- Gandy, Sam. "Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis." Molecular Neurodegeneration. 9 (2014), 1-21.

- McKee, Ann C. "The neuropathology of chronic traumatic encephalopathy." Brain Pathology (Zurich, Switzerland). 25 (2015): 350–364.

- Mez, Jesse. "Chronic traumatic encephalopathy: Where are we and where are we going?" Current Neurology and Neuroscience Reports. 13 (2013), 1-23.

- Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

- Turner, Ryan C. “Modeling chronic traumatic encephalopathy: The way forward for future discovery.” Frontiers in Neurology. 6 (2015), 1-18.

4. Avoidance of full-contact sports
    - Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

    - Lipton, Michael L. “Soccer heading is associated with white matter microstructural and cognitive abnormalities.” Radiology. 268 (2013), 850–857.

    - McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

    - Omalu, Bennet. “Chronic Traumatic Encephalopathy in a national football league player.” Neurosurgery. 57 (2005), 128-134.

VI. Personal opinion
1. Questions for further research
    a. What areas should receive further research?
    b. Should full-contact sports be banned?
2. Pros and cons of current research
    a. Low coverage for all age ranges and sexes
    b. Sample sizes and types of studies

VII. Conclusion
- Barrio, Jorge R. “In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging.” Proceedings of the National Academy of Sciences of the United State of America. (2015), 2039-2047.

- Gandy, Sam. “Chronic traumatic encephalopathy: Clinical-biomarker correlations and current concepts in pathogenesis.” Molecular Neurodegeneration. 9 (2014), 1-21.

- McKee, Ann C. “The spectrum of disease in chronic traumatic encephalopathy.” Brain: A Journal of Neurology. 136 (2013), 43-64.

I. Abstract

Increased media coverage on the potential risk of full-contact sports related concussions leading to Chronic Traumatic Encephalopathy (CTE) has led to a proactive response within the scientific community. Scientists are in search of a way to diagnose and prevent the spread of this neurodegenerative disease. In the past, diagnosis of CTE was primarily confirmed by an extensive autopsy of the brain with a considerable amount of tau protein being a strong indicator of CTE. Finding new biomarker imaging tools to assess an individual's brain prior to death is greatly needed. In the past few years, newly developed tau protein probes have been made available for imaging use in the area of neurodegenerative diseases. In comparison to prior pathological histology findings present in CTE diseased brains, the biomarker probes were found to illuminate tau aggregates in the brain with similar correlating patterns to prior autopsy reports. Biomarkers are available for use in both imaging and blood serum/ cerebrospinal fluid assays for identifying tau protein. Further research in these areas is warranted as the definition and clinical symptoms of CTE become clearer.

Keywords: Chronic Traumatic Encephalopathy (CTE), biomarkers, neurodegenerative disease, tau protein, and traumatic brain injury.

II. Introduction

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease that is quickly becoming associated with full-contact sports (McKee et al, 2009). Countless reports of suicide or premature death are currently being reported in football players, most of which were concluded to have CTE (New York Times, 2016 adaptation of McKee et al 2012). It has become clear that pre-diagnostic imaging tools are needed for earlier detection in high risk populations (Gandy et al, 2014). The use of biomarker imaging tools, blood serum and cerebrospinal fluid assays, with different brain scanning techniques are mostly ready for use (Barrio et al, Gandy et al, Rubenstein et al, Adam et al, Lipton et al). Imaging techniques combined with established autopsy findings and patient history will have a profoundly positive effect in the development of an accurate diagnosis for CTE.

III. CTE

1. What is CTE?

Chronic Traumatic Encephalopathy is an advancing neurodegenerative disorder that can be characterized by an abundance of hyperphosphorylated tau protein, also referred to as p-tau (Stern et

al, 2013). Tau protein accumulates in specific regions of the brain in the conformation of neurofibrillary tangles as well as around smaller blood vessels in the brain (McKee et al, 2013). CTE is believed to be the result of repetitive mild traumatic brain injury (rMTBI); many individuals suffering from CTE were in an environment that increased the risk for rMTBI to occur (Stern et al, 2013). Suggested environments primarily include full-contact sports, active war zones, and abusive household environments (McKee et al, 2013). CTE is identified by autopsy and familial interviews to determine where an individual lies on the staging scale (McKee et al, 2013). Stages are listed in severity from least to greatest in an I-IV numbering method; this corresponds with level of tau formation, behavioral/ cognitive changes and observed gross pathological findings (McKee et al, 2013).

a. Discovery of CTE

In 1928 the precursor to what would be known as CTE was discovered as the repetitive brain injury Dementia pugilistica (DP) or commonly called "punch-drunk syndrome" (Saing et al, 2012). Dementia pugilistica was originally identified in professional boxers who were experiencing noticeable cognitive deficits following repetitive hits to the head during their careers (McKee et al, 2009). Autopsy reports of one boxer suspected of DP showed that the individual's brain exhibited pathologically relevant amounts of neurofibrillary tangles and tau in various conformations (Saing et al, 2012). Tau protein aggregates were found in the frontal, temporal and parietal lobes and regions deep to the cerebral cortex of the brain (Saing et al, 2012).

In the past, DP was only associated with boxers which limited the range of sports where DP could occur (McKee et al, 2009). Recently, American football players have complained of similar cognitive deficiencies; which upon autopsy have presented with pathologically relevant levels of tau protein in various regions of the brain (McKee et al, 2009). Brains investigated for CTE have extended the definition of activity types which are higher in risk for mTBI (McKee et al, 2009). Areas associated with mTBI risk now include a large variety of full-contact sports, active military experiences, and cases of abuse (McKee et al, 2009). Presence of hyperphosphorylated tau tangles are now a primary indicator of CTE in the brains of most deceased athletes with a history of repetitive mTBI (McKee et al, 2009). It is not difficult to envision how observations of clinical manifestations of DP in

individuals not associated with boxing could lead to further investigations as to a potential cause (Saing et al, 2012, McKee et al, 2009).

b. Neurodegenerative disease

In order to understand the effects of CTE as a neurodegenerative disease it is important to evaluate possible risks that are associated with mTBI's. Potential links between other major neurodegenerative diseases, such as Alzheimer's, Parkinson's, frontotemporal dementia and amyotrophic lateral sclerosis, and mTBI have been evaluated (Gardner et al, 2015). Minimal studies performed and mixed findings have left the answer to this hypothesis mostly incomplete (Gardner et al, 2015).

Neurodegeneration presented in one study from football player autopsies found an increase in the players suffering from neurodegenerative diseases at time of death, but were pathologically identified as major dementias (Gardner et al, 2015). Variability in patient to patient clinical presentation or autopsy report have made it difficult to determine how cause and effect are correlated.

Despite a lack of clarity between how mTBI may affect the development of CTE, gross anatomical pathological findings do indicate that neurodegeneration does occur in CTE although severity is dependent on the progressed stage (McKee et al, 2015). In earlier stages of CTE (Stage I and Stage 2), gross anatomical changes are minimal if presenting; in particular enlargement of the lateral ventricles and visualization of the cavum septum pellucidum are observed (McKee et al, 2015). Severe cases of CTE display more advanced gross pathology indicating atrophy, fenestrations and enlargement of the ventricles (McKee et al, 2015).

CTE is not based solely on the findings of gross pathology, but rather the accumulation of tau protein (McKee et al, 2015). Tau observed throughout the four stages can be seen as sparse to extensive within gray matter of the brain (McKee et al, 2015). It is clear that neurons are subject to tau formation even in Stage I (McKee et al, 2015). Clinically presented symptoms are a result of the gross anatomical changes and accumulation of tau in the brain, although confirmation of CTE is still only possible through autopsy (McKee et al, 2015).

c. Discovery of Tau in CTE

A study conducted by Corsellis *et al* examined CTE in the brains of boxers who were of advanced age prior to death (Corsellis et al, 1973, McKee et al, 2015). Current research has expanded upon prior

studies where neurofibrillary tau tangles had presented in the brains of boxers suspected of having Parkinson's and dementia (Corsellis et al, 1973, McKee et al., 2015). Corsellis *et al* established a currently used criteria of relevant pathological findings of CTE in the brain (Corsellis et al, 1973, McKee et al, 2015). Boxers were still the primary focus of most researchers at the time and it took slightly over three decades for other full-contact sports to be evaluated. In 2005, a study regarding the autopsy of a football player with suspected CTE displayed two conformations of tau proteins along with extensive amyloid plaques (Omalu et al, 2005). In this case the gross pathology of the brain was not overtly presenting, however it is not uncommon in the autopsied brains of football players that gross pathology is minimal while tau aggregates are typically more clinically relevant (McKee et al, 2009, Omalu et al, 2005). Inclusion of amyloid plaques in the histological findings of a CTE brain are a result that is typically indicative of Alzheimer's Disease (McKee et al, 2009, Omalu et al, 2005). Which meant that further research to establish a distinguishable difference between CTE and other neurodegenerative diseases was necessary (McKee et al, 2009, Omalu et al, 2005). Autopsy of a brain with DP revealed that the frontal, temporal and parietal neocortices contained aggregates of neurofibrillary tau tangles as well as in regions of the midbrain and cerebellum (Saing et al, 2012). Similar to the findings in 2005 amyloid plaques were present but in lesser quantities (Saing et al, 2012). In order to distinguish DP further from Alzheimer's disease histological staining's of β-amyloid plaques and tau tangles were presented for DP, Alzheimer's disease, Frontotemporal dementia and one control (Saing et al, 2012). Imaging showed distinct patterns between the three pathologies and revealed differences in tau types; Alzheimer's disease associated tau proteins were typically located closer to amyloid plaques rather than randomly dispersed (Saing et al, 2012). However, in the CTE brain it was noted that developing tau proteins as well as mature tau proteins were evident which was used to indicate progression of the disease (Saing et al, 2012). One clarification for the difference between CTE and Alzheimer's disease may come from further research on amyloid plaques (Johnson et al, 2012). Johnson and colleagues noted that prior research indicated that following a traumatic brain injury amyloid plaques can form acutely (Johnson et al, 2012). Findings also revealed that in patients with a history of a single mTBI extensive tau formation had developed within 30% of younger brains (Johnson et al, 2012). In addition, the Alzheimer's disease APOE genotype allele's ε3 and ε4 along

with the other four genotypes are indicated if they are expressed (Omalu et al 2005, Stern et al 2013). APOE allele ε4 is of significant interest for amyloid plaque development due to a link with Alzheimer's related dementia and an association with risk for longer and more severe experiences with mTBI (Stern et al, 2013). CTE as a tauopathy has distinguishable characteristics that help with eliminating other neurodegenerative disorders with similar clinical symptoms. (McKee et al, 2015).

d. Tauopathy

Tauopathies are the result of normal tau protein functions becoming distorted due to phosphorylation (Williams et al, 2006). In a healthy human body, tau proteins exist as assistants to microtubule formation in the brain (Williams et al, 2006). Neurodegenerative disease effects tau protein function, which leads to aggregation of tau protein resulting in an inability to clear these formations (Williams et al, 2006).

1. Tau Protein

Normal tau protein is mapped to the MAPT gene located on chromosome 17 (Lucke-Wold et al, 2014). MAPT codes for six isoforms of tau proteins which is displayed by numbers of repeats which are edited by the splicing of exons; repeats 3R and 4R are combined towards the C-terminus of the peptide chain (Lucke-Wold et al, 2014). One specific variant of splicing exons, exon 10 splice known as hTau40, has been correlated with neurodegenerative diseases (Lucke-Wold et al, 2014). 3R and 4R tau repeats are normally observed in a balanced ratio (Lucke-Wold et al, 2014). An exon 10 splice dictates an imbalance leading to an overexpression of 3R tau repeats that are observed in neurodegenerative disorders (Lucke-Wold et al, 2014). CTE tau repeats are more prevalent in the 4R variation (McKee et al, 2015).

Two types of tau are observed T-tau and P-tau, with T-tau being the Total tau found in neurons and P-tau being an activated form of tau through phosphorylation (Rubenstein et al, 2015). Excessive phosphorylation of several known sites of serine and threonine in the tau peptide are regarded as areas where once they are activated will create neurofibrillary tangles (Rubenstein et al, 2015). Additionally, increased activity of histone deacetylase causes an increase in P-tau formation which results in the formation of tau aggregates (Cook et al, 2014). Without external aid from an inhibitor for histone deacetylase, accumulated tau protein cannot be dephosphorylated

(Cook et al, 2014, Rubenstein et al, 2015). Buildup of tau protein leads to the formation of neurofibrillary tangles; growth occurs in stages where maturity is identified by acetylated lysine residue 280 (Lucke-Wold et al, 2014).

Traumatic brain injury can induce axonal and vascular injuries (McKee et al, 2015). During this time, levels of P-tau and T-tau become significantly detectable in cerebrospinal fluid and blood serum (Rubenstein et al, 2015). Tau was traced for three to six months in certain patients with severe traumatic brain injury by Rubenstein *et al*. Initial levels of P- and T-tau were higher, however T-tau was able to return to normal range while P-tau remained evident even at the end of the trial (Rubenstein et al, 2015). Extensive P-tau pathology has been observed in autopsy based research and is a strong indicator of CTE development (McKee et al, 2015).

e. Other potentially associated proteins and risks for neurodegenerative disease

1. TDP-43

Transactive response DNA-binding protein 43 (TDP-43) is a microscopically presenting protein in CTE and other neurodegenerative diseases (McKee et al, 2010, Saing et al, 2012). TAR-DBP is the gene responsible for encoding TDP-43 on chromosome 1 (McKee et al, 2010). Primary function of TDP-43 involves acting as a cytoskeleton binding protein and a transcription stabilizer for mRNA (Costanza et al, 2011). Damage to axonal cytoskeletons during traumatic brain injuries is proposed to lead to the activation of TDP-43 proteins as a repair response (Costanza et al, 2011). TDP-43 activation is initiated when TDP-43 C-terminus undergoes cleavage resulting in fragmentation (Lucke-Wold et al, 2014). However, extensive autopsy reports have shown that Fragmented TDP-43 tends to accumulate rather than displaying proper repair mechanisms, leading to a similar outcome as tau aggregation resulting in toxicity (McKee et al, 2010, Lucke-Wold et al, 2014, Costanza et al, 2011). TDP-43 aggregation can lead to a blockage of RNA activities as well as introducing errors into cellular processes which can lead to increased free radical activity (Lucke-Wold et al, 2014). Tau neurofibrillary tangles with close TDP-43 pathology are occasionally observed in autopsies (Saing et al, 2012). TDP-43 was also expressed in the brains of 80% of athletes who were also diagnosed with CTE in a particular autopsy report (McKee et al, 2010). How TDP-43 operates with regard to neurodegeneration is not entirely known, however

further investigation of this protein could lead to better insight regarding tauopathies such as CTE (McKee et al, 2010).

2. β-Amyloid

β-amyloid plaques are a clinically relevant identifying protein for a diagnosis of Alzheimer's disease, it has also recently been observed in early stages of traumatic brain injury (Johnson et al, 2012). A potential mechanism for β-amyloid plaque formation involved with traumatic brain injury is likened to the development of tau; where the process by which pre-amyloid proteins has been altered due to a traumatic event (Omalu et al, 2005). It is proposed that CTE and Alzheimer's disease may enhance the development of one another or follow the same chemical pathways using similar proteins (Costanza et al, 2011). β-amyloid plaques can potentially be distinguished between cases of Alzheimer's disease and traumatic brain injury. In cases where the plaques presenting lack Alzheimer's disease specific tangles can act as a potential eliminating technique for ruling out sporadic Alzheimer's disease from a list of suggested pathologies (Omalu et al, 2005). β-amyloid, in traumatic brain injuries, also has a different pattern of plaque development than most cases of Alzheimer's disease (Johnson et al, 2012). Plaques associated with traumatic brain injury exhibit extensive formation throughout the cortex and in greater amounts (Johnson et al, 2012). Short-lived β-amyloid plaque formation has been observed in younger individual's following a traumatic brain injury (Johnson et al, 2012). There are discrepancies between researchers as to whether β-amyloid is presented in CTE. In cases regarding traumatic brain injury the presence, absence or association of neurofibrillary tangles and plaques leaves β-amyloid as a protein to be further investigated (Johnson et al, 2012 Omalu et al, 2005, McKee et al, 2010). The involvement of β-amyloid is not a common hallmark of CTE although it has presented in autopsy reports (McKee et al, 2010).

3. α-Synuclein

Parkinson's disease is histologically hallmarked by the presence of α-Synuclein positive Lewy bodies (McKee et al, 2013, Omalu et al, 2005, Saing et al, 2012). However, in at least two autopsy studies, patients with pre-mortem diagnosis of Parkinson's disease revealed that the brain

was negative for Lewy body staining (Omalu et al, 2005, Saing et al, 2012). In more extensive research, findings of Lewy bodies in older patients was not uncommon, and was considered a co-morbid finding of CTE with another neurodegenerative disease (McKee et al, 2013). Patients presenting with Parkinsonian symptoms should receive a full evaluation including any prior mTBI events in order to properly diagnose this neurodegenerative disease.

Autopsy diagnosis of CTE in brains of athletes has revealed that 37% had some other neurodegenerative disorder (McKee et al, 2013). One potential theory regarding α-Synuclein development in brains with CTE is the possibility that a chemical pathway is activated by mTBI (McKee et al, 2013). A secondary theory is that tau protein might promote abnormal protein growth as it accumulates, triggering this event (McKee et al, 2013). Traumatic brain injuries have been suggested to play a role in instigating cases of neurodegeneration and leading to the formation of abnormal protein development (Omalu et al, 2005, McKee et al, 2013). These findings support the need for patient history evaluations for mTBI in order to accurately diagnose neurodegenerative disorders.

f. Prion theory

As research continues to investigate proteins, such as tau, α-synuclein, or β-amyloid, and the role that is played in neurodegenerative disorders, a cause and effect relationship has been proposed by the prion theory of abnormal protein development (Prusiner, 2013). Formation of prions occurs through conformational changes to normal proteins that begin to self-replicate (Prusiner, 2013). Discovery of β-amyloid in experiments with Scrapie, a virulent prion infection, lead to the idea that certain proteins may be prions themselves (Prusiner, 2013).

In general, most cases of neurodegenerative disorders can be determined through genetic testing. Inheritance of a prion based neurodegenerative disease is actually a smaller risk, of 10-20%, when compared to the 80% of cases that arise sporadically (Prusiner, 2013). It is presumed that most neurodegenerative disorders arise from sporadic development (Prusiner, 2013).

The mechanism by which tau protein presumes a prion function in the brain in not completely understood (Prusiner, 2013). Experimentation with murine and bacterial models have shown that tauopathies can spread from cell to cell, and that in certain areas of the brain, such as the hippocampus

and striatum, specific patterns of tau fibrils arise (Prusiner, 2013). When investigating CTE it could be useful to examine the tau as a prion theory.

2. Current theory of causation

Repetitive mTBI is the current proposed mechanism for CTE development in the brain (McKee et al, 2013). Frequent impacts to the brain are believed to activate the formation of hyperphosphorylated tau which spreads throughout the brain leading to mass neurodegeneration (McKee et al, 2013). Currently it is difficult to determine whether a single concussive event or multiple events are needed to actually initiate neurodegenerative disease development (Gardner et al, 2015). It is also difficult to determine every type of environment, and with what frequency where multiple concussive events could occur (Gardner et al, 2015).

3. When does CTE develop?
   a. Later stages of life

CTE development does not overtly present itself following an episode of mTBI (Costanza et al, 2011). Typically, CTE presents as behavioral impairments in the middle aged (Mitsis et al, 2014). The time for CTE to become clinically noticeable is thought to be caused by the changes to tau protein which may take years to fully display cognitive impairment (McKee et al, 2009). Since the effects of the damage are ongoing following the event, it is perceived that the longer an individual lives the more severe the neurodegeneration (McKee et al, 2009).

   b. General age range

CTE clinical symptoms typically begin in a range of 30 to 65 years of age, although deviations have occurred with presentation in cases of younger and older patients (Mez et al, 2013). Behavioral symptoms usually precede cognitive decline as the stages of CTE progress (Mez et al, 2013). CTE dementia development does not proceed as quickly as it does with Alzheimer's patients, although it is noted that this type of dementia is no less severe (Mez et al, 2013).

4. Details of injury and how CTE is caused
   a. Concussive vs. sub-concussive injury

Concussions, or mTBI, are the result of high impact forces directed towards the brain or areas that are connected to brain function where loss of consciousness may or may not occur

(Costanza et al, 2011). Primary damage sustained by a concussive event is directed towards brain function (Costanza et al, 2011). A Glasgow Coma Scale is clinically used to determine an incident of mTBI, and a score of 13-15 is considered a positive for concussion (Gardner et al, 2015). Sub-concussive events do not elicit clinical symptoms at the acute stage but are still caused by an impact to the skull (Gardner et al, 2015). CTE is thought to be primarily caused by repetitive concussive events (Gardner et al, 2015).

b. Single vs. multiple injuries

CTE is currently linked to repetitive mTBI, however autopsies of individuals with a history of only one mTBI have some interesting developments (Johnson et al, 2012). Postmortem studies of brains that experienced an mTBI within a 1-47-year range, prior to death, were inspected for differences in tau and β-amyloid production compared to normally aged control brains (Johnson et al, 2012). 34% of individuals under the age of 60, who lacked age dependent pathology, that had experienced a singular mTBI event displayed neurofibrillary tau formation (Johnson et al, 2012). Clusters of tau exhibited were not exhibited in the same patterns as control group findings, and typically mTBI evaluations displayed more pathological findings than the control group (Johnson et al, 2012). Johnson and associates determined that patients that survived a single mTBI event would present a vast tau distribution when compared to normally aging controls (Johnson et al. 2012). Since tau does not appear rapidly after one traumatic brain injury a neurodegenerative process may be involved, which was similar to findings with CTE (Johnson et al, 2012).

Multiple traumatic brain injuries are an unavoidable part of many full contact sports and not limited only to boxing. In the case of a patient who had been a heavy-weight boxer for 13 years who displayed extensive development of tau in the frontal lobe was diagnosed with DP

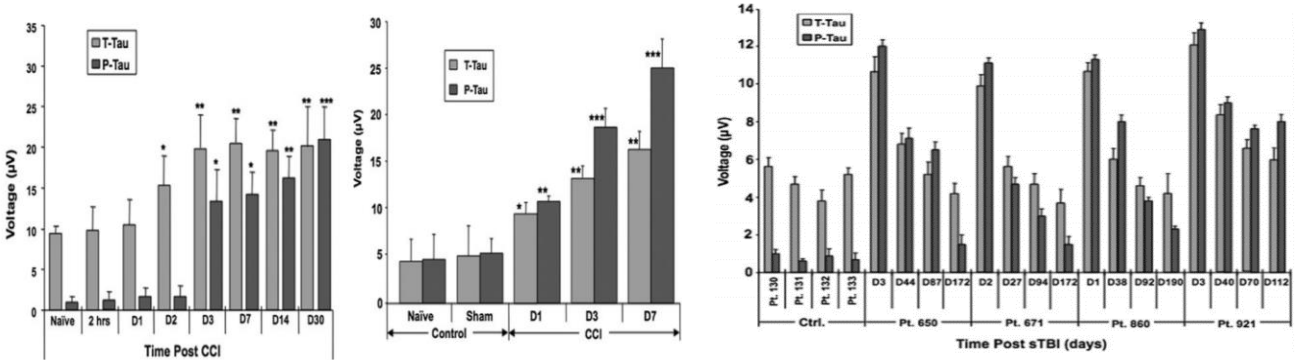

Figure 1. Comparison on murine and human tau blood serum assay levels following a severe traumatic brain injury [from left to right: mouse, rat, and human] (adapted from Rubenstein et al, 2015).

(Saing et al, 2012). Further investigation of full-contact sports, such as football, soccer, boxing and martial arts, as well as military personnel found evidence of CTE when repetitive trauma had occurred (McKee et al, 2009).

CTE development may have a stronger relationship with repetitive trauma, although severity of trauma and number of traumatic injury events still remains in question (Gardner et al, 2015). While pre-diagnostic tools, used for mTBI, will not fully indicate a diagnosis of CTE it could be helpful for acute diagnosis of injury as a preventative assessment. Real time diffusion tensor imaging used on active military personnel within a week of injury displayed slight signal loss in the white matter of the brain, more specifically the superior longitudinal fasciculus in some participants (Adam et al, 2015). Furthermore, detection of elevated p-tau in blood serum and cerebrospinal fluid had a positive correlation with mTBI, and could be used as an identification tool if a traumatic brain injury is suspected (Rubenstein et al, 2015). It would be beneficial to evaluate mTBI data from acute to chronic stages of injury for a full understanding of the pathology as it develops.

c. Force trauma data

1. Murine models

Rodent models have provided significant details on traumatic brain injury when compared to human data, either from autopsy or from acute clinical findings. Data were collected from the blood serum and cerebrospinal fluid assays of patients presenting with severe traumatic brain injury symptoms (Rubenstein et al, 2015). Samples were compared with rodent brain tissue extracts following impact induced trauma to the brain (Rubenstein et al, 2015). Rodent model brains experienced an impact speed of 4.5 m/sec with a 1.5 mm impact depth from a 3.5 mm impactor tip for mice, and a 2.5 mm impact depth from a 5 mm impactor tip for rats (Rubenstein et al, 2015). Rodent tissue and blood

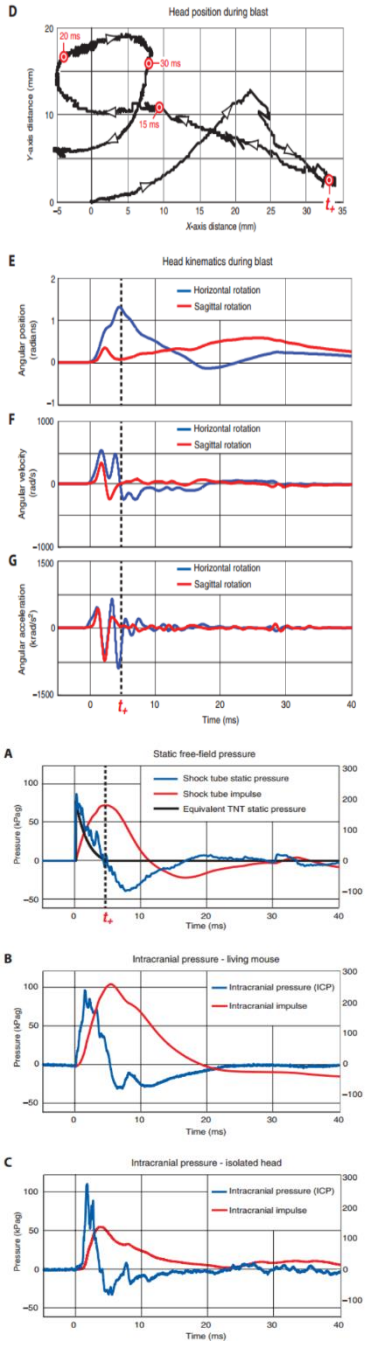

Figure 2. Murine model observed intracranial pressure, head rotation and kinematics following a reproduction of an explosive blast wave (Goldstein et al, 2012).

samples were assessed at 7 days and 30 days for mice and rats respectively (Rubenstein et al, 2015). Patients were evaluated for the first 7 days for cerebrospinal fluid changes and blood serum changes were assessed at one, three and six month intervals following a severe brain injury (Rubenstein et al, 2015). T-tau is the total tau in the central nervous system and P-tau is the tau responsible for normal microtubule structuring (Rubenstein et al, 2015). Figure 1 displays how the tau levels increase in the early stages of the injury event and remain elevated for a significant period of time following the event (Rubenstein et al, 2015). Particularly in humans, the T-tau normalized around one month following the injury, at the six-month marker P-tau levels were still higher than normal controls (Rubenstein et al, 2015). Cerebrospinal fluid tau was similarly elevated in humans during the acute stage following trauma; P-tau levels were increasing in all patients but a patient to patient variability were observed in the elevations of T-tau (Rubenstein et al, 2015). Changes in cerebrospinal fluid or blood serum may be a way to evaluate potential chemical mechanisms for CTE formation although research in the area of acute P-tau levels are further required as the role it has is not fully understood with regards to pathology (Rubenstein et al, 2015).

Blast waves from explosives in a war setting are also being analyzed for a potential link between mTBI and CTE (Goldstein et al, 2012). Goldstein and associates compared the brains of veterans who had been exposed to blast or concussive trauma to mice that underwent shock tube induced blast wave trauma (Goldstein et al, 2012). Autopsy of veterans' brains revealed CTE type damage which included neurofibrillary tau tangles of the perivascular foci and glial tangles specific to sulcal depths in certain regions of the frontal, temporal, and parietal cortices (Goldstein et al, 2012). Damage was observed to vasculature and neural cells were also noted (Goldstein et al, 2012). The mouse model was partly used to examine a link between CTE and blast induced trauma, the other area of concentration was regarding behavioral changes (Goldstein et al, 2012). A needle hydrophone was inserted into the hippocampus of the living mouse to monitor pressure changes during the blast exposure, blast shock waves

were set to match explosives in combat at speeds of 450 m/sec penetrating at depths of 11mm in 24 μsec (Goldstein et al, 2012). Kinematics of the mouse head where tracked by following the nose position during the blast (Goldstein et al, 2012). When kinematics was compared to head positioning there was an observed increased initial pressure during time of impact with head positioning sharply jerking forward then back before completion of rotation (Goldstein et al, 2012, see Figure 2). Neuropathological findings in mice were similar to CTE type trauma exhibited in the brains of military veterans, which included tau pathology in neural cells with phosphorylated and pre-tangle tau detected without the presence of matured tau (Goldstein et al, 2012). Neural cell changes will be discussed briefly in section 5 of this paper.

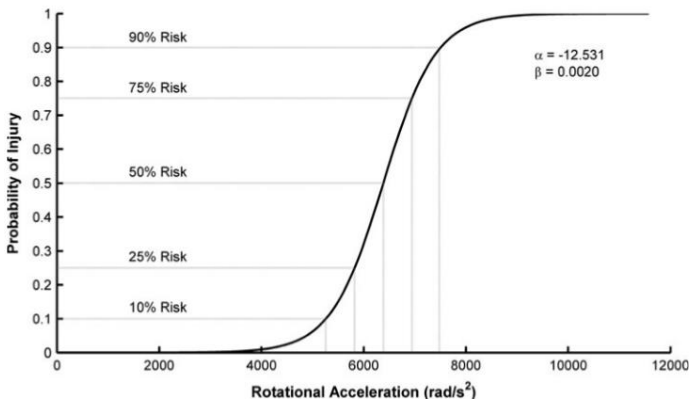

Figure 3. Risk of injury compared to rotational accelerations in football players (Rowson et al, 2011).

2. Human accelerometer data

Football players are a large at risk group for sports related concussions. Three college football teams, Brown, Dartmouth and Virginia Tech, gave informed consent to wear accelerometer tracking devices to measure real time head accelerations for impact data (Rowson et al, 2011). Football players were affixed with accelerometers in their helmets, 314 players wore the Head Impact Telemetry (HIT, 6 accelerometers) model and 21 players wore the 6 Degrees of Freedom (6DOF, 12 accelerometers) accelerometers during practices and game play (Rowson et al, 2011). The accelerations measured head rotation by remaining contact with the player's head, and exceeding threshold of a normal hit was determined to be 14.4 g's (Rowson et al, 2011). 300,977 head impacts were tracked with a total of 57 concussions observed (Rowson et al, 2011, see table 1.). HIT

tracked accelerations were observed with mean values of 1230 ± 915 rad/s^2 for sub-concussive rotational accelerations and 5022 ± 1791 rad/s^2 for concussive rotational acceleration data (Rowson et al, 2011). 6 Degrees of Freedom accelerometer rotational accelerations were only available for sub-concussive impacts with mean of 1158 ± 972 rad/s^2 (Rowson et al, 2011). There was increased risk of injury associated with larger rotational accelerations as depicted in Figure 3 (Rowson et al, 2011). It was observed that concussive outcomes where a result of the physical impact trauma to the brain (Rowson et al, 2011). The accelerometer data could direct further research in finding new equipment for athletes and determining high risk positions in game play.

Head impact data	Plane of rotation	Sub-concussive	Concussive
Front/Back of helmet	Primarily sagittal	67.5% , 193,465 hits	47.9% , 33 hits
Side of helmet	Coronal	17.3% , 49,645 hits	12.3% , 7 hits
Top of helmet	Linear	15.2% , 43,526 hits	29.8% , 17 hits

Table 1. Recorded impact data with plane of rotation compared to positioning of impact (adapted from data observed by Rowson et al, 2011).

d. Who it affects and associated risk

Full-contact sports are currently gaining the most attention with regards to CTE. Many athletes whose brains were diagnosed with CTE began playing sports between 11 and 19 years of age (McKee et al, 2009). Risks for CTE development due to environment are significantly higher for athletes and soldiers (Lucke-Wold et al, 2014). Both groups have been known to have behavioral and psychological changes one year after a traumatic brain event (Lucke-Wold et al, 2014).

1. Athletes

Football player's position, which included offensive linemen, defensive linemen and linebackers, were associated with significant risk of behavioral changes and cognitive decline (McKee et al, 2009). Soccer players were studies in attempt to establish a relationship between neurocognitive decline and the number of times players headed a ball (Lipton et al, 2013). Soccer balls intercepted by "heading" can travel at speeds of 30 m/sec during practice

drills, or up to 80 m/sec during a game (Lipton et al, 2013). Players that had an average soccer career of 22.4 years were estimated to have headed a ball 432 times in a year on average (Lipton et al, 2013). A determined threshold upon evaluation of number of heading events, and cognitive scores determined that the threshold for changes in cognition was around 1800 headings per year (Lipton et al, 2013). Diffusion tensor imaging data display a temporo-occipital white matter with a contrecoup injury type, changes observed in the white matter where opposite the site of impact (Lipton et al, 2013). In boxers, symptoms of concussive damage became apparent by observed decrease in speed of movement and fighting skills during a fight (Costanza et al, 2011). Increased blows to the head and lowered skills leaves a boxer exposed to further trauma (Costanza et al, 2011). While CTE development is not limited to football, boxing or soccer traumatic findings from these sports have been applied when covering potential risks for other full-contact sports.

2. Military personnel

In active combat, soldiers are at a significantly high risk for blast-exposure mTBI (Adam et al, 2015, Goldstein et al, 2012). Goldstein and associates force trauma data, mentioned extensively in the force trauma section, showed that autopsied brains of veteran's displayed neuropathological changes indicative of CTE (Goldstein et al, 2012). Diffusion tensor imaging conducted by Adam *et al* indicated that following a single traumatic brain event changes to the white matter of the brain could be observed in acute stages of injury (Adam et al, 2015). In no certain terms does this information sully the honor of veteran's or current military personnel. However, this does indicate a need for better protective gear for the men and women who serve our country.

3. Victims of abuse

Cases of abuse may sporadically enter the world of news, but the effects of abusive trauma are not widely publicized. McKee and associates added a prior case study of a woman who had suffered severe abuse from her spouse, clinically she was assessed with dementia where autopsy later revealed findings of neurofibrillary tangles similar to those found in boxers (McKee et al, 2015). One questionnaire based study evaluated a

group of school children for traumatic brain injury in comparison to the Conners Parent Rating Scale which would indicate problem children (Dams-O'Connor et al, 2014). 44% of children reported a traumatic brain event while 10% where positive for chronic traumatic brain injury (Dams-O'Connor et al, 2014). 79% of the chronic cases exhibited a positive Conners rating and 80% of the chronic cases found a decline in cognitive function (Dams-O'Conner et al, 2014). Juvenile delinquents in the juvenile justice department of El Paso were among another group to take the traumatic brain injury questionnaire (Dams-O'Connor et al, 2014). 271 juveniles were assessed for traumatic brain injury and 76% of these individuals admitted to experiencing one traumatic brain injury (Dams-O'Connor et al, 2014). It was noted behavioral changes and an increased level of delinquency are associated with an experience of a traumatic brain injury (Dams-O'Connor et al, 2014). It should be further noted that abusive environments are a primary risk to the victim although in some cases escape from trauma may be unachievable.

5. Other potential contributory factors to CTE development
   a. Age

A diagnosis of CTE in the aged has proven difficult due to the fact that risks for neurodegenerative diseases tends to increase over time (Maroon et al, 2015). Age related risks may explain the compounded findings of CTE with signs of other neurodegenerative disorders that add to the difficulty of a true CTE diagnosis (Maroon et al, 2015). Data regarding CTE development as a whole process is also limited to stages of development (Maroon et al, 2015). Brain injuries in the aged are regarded as severe with acute stages of injury displaying signs of cognitive impairment and neurotrauma (Turner et al, 2015). Trauma to the brains of younger individuals is subject to extreme debate (Mez et al, 2013). Researchers speculate that brain plasticity should elicit a better recovery time, while others propose that immature brains are at risk of improper development following a concussion (Mez et al, 2013). What is clear is that the lack of data regarding CTE in an extensive array of ages is needed in order to understand full progression of the disease (Turner et al, 2015).

b. Sex

In general, a large amount of CTE reported data involves male participants, however data regarding concussion recovery and potential CTE development is needed (Mez et al, 2013). Female athletes tend to experience stronger and more frequent concussion rates when compared to males (Mez et al, 2013). Estrogen has been known to display protective mechanisms for immune function when in higher circulating concentrations (i.e. pregnancy levels of hormone) (Kovacs et al, 2002). The exact relationship between estrogen and immune response is not fully understood (Kovacs et al, 2002). Female mice displayed a 10-fold increase in concentration of estrogen when compared to males in response to burn trauma (Kovacs et al, 2002). A delay in the onset of immune sensitivity was also expressed in female mice, compared to the rapid onset of immune function by males, which was proposed to imply a cytokine neutralizing survival technique (Kovacs et al, 2002).

Cortical contusions, as a result of mTBI, measured in female rats were of smaller volume than their male and ovariectomized female counterparts (Bramlett et al, 2001). The difference in contusion volume was attributed to endogenous hormonal protection provided in normal female rats (Bramlett et al, 2001). Estrogen and progesterone were considered the most probable reasons for cerebral protection (Bramlett et al, 2001).

6. Parts of the brain affected by CTE
   a. Multiple gross anatomical regions of the brain

Omalu *et al* presented the first case report regarding the potential substrate responsible for CTE which resulted in a finding of tau protein with β-amyloid plaques in the brain of a deceased NFL player (Omalu et al, 2005). In terms of gross pathological findings staining revealed little to no atrophy which could not be explained by aging (Omalu et al, 2005). Specialized staining procedures revealed abnormal protein development in the frontal, temporal, parietal, occipital, cingulate cortex and the insula (Omalu et al, 2005). It is possible that the progression of CTE in this individual was at a less severe stage of development due to further findings of affected structures by McKee and associates (McKee et al, 2013). In a larger study, the extent of gross pathological findings was determined by a categorizing of stages of development with an I-IV method (McKee et al, 2013). Brains used for this autopsy ranged from ages 14-98 years old

	Gross	Tau	Other	Clinical symptoms
Stage I	None	NFTs at depths of cerebral sulci of the frontal cortex	TDP-43 inclusions within sub-cortical white matter and fornix	Mostly pre-clinical Some insidious symptoms like headache, depression, attention loss
Stage II	Mild enlargement of lateral and 3rd ventricles Cavum septum pellucidum Pallor of LC and SN	NFT in subcortical white mater, medial temporal lobe, brainstem	Rarely amyloid beta found	Pronounced behavioral/personality changes Short term memory loss
Stage III	Reduced brain weight Mild frontal/temporal atrophy	NFTs present diffusely in frontal, temporal and parietal cortices. Often concentrated around small vessels and depths of sulci	TDP-43 inclusions now present in cerebral cortex, medial temporal lobe, diencephalon, and brainstem	Memory loss, overall cognitive impairments Aggression, mood disorders
	Enlargement of lateral and 3rd ventricles Pallor of LC and SN Atrophy to mammillary bodies, thalamus, hypothalamus, thinning of corpus callosum	NFTs present in subcortical structures: hippocampus, entorhinal cortex, amygdala, Nucleus Basalis of Meynart, LC, hypothalamus, mammillary bodies, SN, Raphe nuclei. Rarely present in spinal cord and dentate nucleus of cerebellum	Aβ in 13% of cases	75% considered cognitively impaired
Stage IV	More pronounced reduction in brain weight More pronounced atrophy to frontal, temporal lobes and anterior thalamus 2/3 subjects have septal abnormalities Generalized WM atrophy LC and SN now pale	Widespread degeneration resulting from severe NFT deposition. Greater NFT inclusion of cerebellum and medulla Prominent myelin loss and astrocytosis of WM in cerebral cortex	TDP-43 deposition is more widespread and severe Neuronal loss in SN Severe spongiosus of cerebral cortex and widespread neuronal loss	Cognitive impairments Severe mood disorders Language difficulties Visuospatial difficulties Gait/motor control impairments.

Abbreviations: Aβ LC, Locus Coeruleus; NFT, Neurofibrillary Tangle; SN, Substantia Nigra; WM, White Matter.

Table 2. Summary of CTE stages of development attributed to autopsy research by McKee *et al* (2013). (Table adapted by Sundman et al, 2015).

(McKee et al, 2013). The stages build upon one another so that as the stages increase in severity the number of affected locations tend to increase (McKee et al, 2013).

Neurons require oxygen via endless blood flow from nearby capillary beds in order to create energy required for cellular respiration (Doshi et al, 2015). When mTBI occurs there is a chance of vascular damage leading to a change in blood flow which could cause regional oxygen level variations (Doshi et al, 2015). Whether the brain is oxygen starved or in excessive amounts may depend on the time at which the patient undergoes scanning and the severity of the concussive event (Doshi et al, 2015). Changes in oxygenation of brain tissue may explain why tau has been discovered around certain regions of the brain (Doshi et al, 2015, McKee et al, 2015).

Evidence from this report displays the migratory nature of the disease and tau formation. The list of noticeable brain structures effected is substantial. Information from this research has led to an update of the criteria for CTE diagnosis, which would cover a larger array of repetitive mTBI patient types (McKee et al, 2013, Sundman

Figure 4. The stages of tau development in CTE. Hyperphosphorylated tau is indicated by areas with brown staining patterns observed. (McKee et al, 2013).

et al, 2015, see Table 2). In particular, this expands the definition to include hyperphosphorylated tau development on the microscopic level along with gross pathological changes (McKee et al, 2013, see Figure 4).

b. Neural cells

Injuries to the brain that consist of a rapid acceleration-deceleration, and rotational forces creates severe strain on neurons, glial cells, and blood vessels (McKee et al, 2015). Somatic changes in murine neural cells, in the acute stages of a traumatic event, indicate cell death around the impact location, loss of somatic dendrites and a decrease in regional synapses (Goa et al, 2011). In an experiment with blast-induced trauma to mice “dark neurons” were observed near damaged capillaries (Goldstein et al, 2012). Dark staining of the nucleus was a positive indicator of necrotic or apoptotic mechanisms within the cell, which featured a condensed nucleus and an electron-dense cytoplasm (Goldstein et al, 2012).

The most damage was observed in the stretching of axons and blood vessels housed within the perivascular regions and deep in the cerebral sulci near the point of impact (McKee et al, 2015). These injuries lead to axonal sheering cutting off the connection between axon and the soma and a disruption of the blood-brain-barrier which elicits a repair response (Lucke-Wold et al, 2014). Once the axon is cut from the soma the cell will die cutting off links to surrounding cells (Lucke-Wold et al, 2014).

Astrocytes take on the role of notifying the surrounding neurons of pain, activating glial fibrillary acidic protein for microfilament production and activating the release of self-renewing neurospheres (Lucke-Wold et al, 2014). The astrocytes spread out in the white

matter of the brain, particularly in the corpus callosum, motor and somatosensory cortices (Lucke-Wold et al, 2014). Astrocyte activation may also stem from microglia-mediated crosstalk as immune cells release cytokines in response to mTBI (Lucke-Wold et al, 2014). Uptake of the released cytokines initiates the release of reactive oxygen species from the astrocyte which propagates excitotoxicity (Lucke-Wold et al, 2014).

Activation of microglia leads to a stimulation of neuroinflammation as it continues to expand (Lucke-Wold et al, 2014). If the injury is a singular event microglial activation is thought to be a protective mechanism, however neurodegeneration will ensue if multiple injuries occur and could contribute to the formation of glial tangles which will attribute to further long term damage (Lucke-Wold et al, 2014). Microglial release of inflammatory cytokines can also contribute to tissue damage if triggered to do so (Lucke-Wold et al, 2014).

c. Behavioral and cognitive changes

The spectrum of behavioral changes observed in athletes may be dependent upon type of traumatic contact in sport (McKee et al, 2009). Clinically presenting symptoms of CTE could involve any of the symptoms seen in Table 2. (McKee et al, 2009, Sundman et al, 2015). CTE behavioral presentations in boxers is often hallmarked by increased apathy when compared to other CTE-sport related behavioral changes (Gandy et al, 2014). Military personnel and other full-contact athlete types tend to exhibit aggressive or depressive behaviors, which could be attributed to illegal substance abuse (Gandy et al, 2014). Changes in behavior and executive function depend on where in the brain CTE damage was found (McKee et al, 2013, Sundman et al, 2015, Table 2). A recent proposal to explain the reason why some individuals, with a known CTE diagnosis, are more prone to either cognitive decline or behavioral changes was that there could be two different phenotypic expressions in developing CTE (Stern et al, 2013). The behavior/mood group was characterized by aggression or depression found at younger ages (Stern et al, 2013). Cognitive decline developed at a later period (Stern et al, 2013). The cognition group primarily exhibited signs of impaired episodic memory with strong indications of developing dementia (Stern et al, 2013). Table 3 further displays

Variable	All symptomatic subjects, % (n = 33)	Behavior/mood group, % (n = 22)[a]	Cognition group, % (n = 11)[a]
Cognitive features			
Memory impairment	84.8	77.3	100
Executive dysfunction	78.8	72.7	90.9
Attention and concentration difficulties	72.7	63.6	90.9
Language impairment	57.6	54.5	63.6
Visuospatial difficulties	54.5	54.5	54.5
Behavioral features			
Explosivity	57.6	72.7[b]	27.3[b]
Impulse control problems	45.5	54.5	27.3
"Out of control"	51.5	63.6[b]	27.3[b]
Physically violent	51.5	68.2[b]	18.2[b]
Verbally violent	48.5	73.6[b]	18.2[b]
Disinhibited speech	0	0	0
Disinhibited behavior	3.0	0	9.1
Socially inappropriate	3.0	0	9.1
Paranoia	18.2	22.7	9.1
Mood features			
Sadness/depression	63.6	86.4[b]	18.2[b]
Anxiety/agitation	15.2	13.6	18.2
Manic behavior/mania	3.0	4.5	0
Suicidal ideation/attempts	30.3	31.8	27.3
Hopelessness	63.6	72.7	45.5
Apathy	6.1	9.1	0

[a] Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.
[b] Statistically significant between-group difference, $p < 0.05$.

Table 3. Differences in initial clinical observation of athletes with a postmortem diagnosis of CTE separated into two clinically presented phenotypes (Stern et al, 2013).

differences between the two phenotypes observed by family member recounts of patient history (Stern et al, 2013).

d. Potential changes in motor function

CTE progression is proposed to have a motor decline element in later stages of disease development (McKee et al, 2009). Typically, this follows behavioral and cognitive impairment and can clinically appear as symptoms of Parkinson's disease (McKee et al, 2009). CTE changes to motor function are associated with length of athletic career and number of sustained brain injuries (McKee et al, 2009). Changes observed are broad, including areas of hearing, gustation, optical, speech and ocular changes having appeared in late stages of the disease (McKee et al, 2009). Impairment to the brain has been associated with tau linked neurodegeneration in the brain which has shown to be extensive at later stages (Gandy et al, 2014, McKee et al, 2009). Chronic traumatic encephalopathy- motor neuron disease (CTE-MND) is a comorbid disease diagnosed when CTE and amyotrophic lateral sclerosis is presented in the spinal cord (McKee et al, 2013). CTE-MND do not clinically present at the same time, rather CTE cognitive and behavioral changes are observed first with MND motor changes soon to follow (McKee et al, 2013). Eight brains in the McKee *et al* autopsy study were found to have CTE-MND; clinical assessment for living individuals should include cerebrospinal fluid biomarkers to determine if a diagnosis of CTE-MND is present (McKee et al, 2013, Gandy et al, 2014).

7. Factors that could interfere with diagnosing CTE

It is not uncommon for patients hospitalized due to concussion to receive IV fluids or opiates (Doshi et al, 2015). In some cases, patients presenting with a concussion may receive a battery of tests for drugs, alcohol and prescriptions as well as painkillers or IV fluids (Doshi et al, 2015). In a study conducted by Doshi *et al* at the acute stage of concussive events displayed that six individuals tested positive for alcohol, cannabinoids, opiates and benzodiazepines (Doshi et al, 2015). Four patients received IV fluid; either normal saline or potassium chloride (Doshi et al, 2015). IV fluid administration could lead to altered data when evaluating cerebral blood flow following a concussive event (Doshi et al, 2015). When a diagnosis of CTE is to be determined clinically it is suggested to get a complete patient history that may include any illicit drug use, alcoholism or anabolic steroid use as there could be a link between substance abuse and P-tau formation in the brain (McKee et al, 2015). Substance abuse has been shown to increase the chance of neurodegenerative disease development which may include tau formation (Maroon et al, 2015). Specifically, in cases of opiate abusers, P-tau aggregates with enhanced conformations have been observed (McKee et al, 2015, Maroon et al, 2015).

8. Assessment tools for CTE development
    a. Past and current confirmed CTE diagnosis

In the initial stages of CTE discovery, when it was labeled as Dementia Pugilistica, neuropathological aberrant protein formation and gross pathological features were determined by autopsy report (McKee et al, 2009, Saing et al, 2012). In fact, autopsy based findings observed by Omalu *et al* diversified another potential sport that could be involved with CTE formation by including American football (McKee et al, 2009, Omalu et al, 2005). In current research extensive autopsy, histological and patient pre-mortem family/clinical history are included for determining a CTE diagnosis (McKee et al, 2009, Omalu et al, 2005, Saing et al, 2012). Unfortunately, a confirmed diagnosis is only confirmed by autopsy reported findings (McKee et al, 2009).

b. Recent contributions to current practices in development

1. Blood serum and cerebrospinal fluid assays

In a recent study evaluating levels of p- and t-tau, following a severe traumatic brain injury, an ultrasensitive immunoassay was used to assess tau in blood serum and cerebrospinal fluid (Rubenstein et al, 2015). Anti-tau monoclonal antibodies and epitopes were used for isolation purposes in assessing levels of tau in the collected fluids (Rubenstein et al, 2015). Enhanced immunoassay multi-arrayed fiberoptics (EIMAF) was used directly along with rolling circle amplification EIMAF for detection of tau in serial dilutions of fluids for increased sensitivity (Rubenstein et al, 2015). Figure 1, exhibited previously in this research, displays the elevated tau findings from this immunoassay (Rubenstein et al, 2015).

2. PET scanning and biomarkers

a. Biomarkers

PET imaging has come to include seven types of biomarkers available for experimental use (table 4) (Dani et al, 2016). Biomarker imaging ligands are being used to illuminate tau protein in the brain. One major benefit of the biomarkers is the ability to find tau protein formation in individuals prior to death (Gandy et al, 2014). Biomarker use applies to many neurodegenerative diseases where it better serves as both a diagnostic and a differential imaging tool. A good example of biomarker use comes from the studies of Dickstein *et al* and Mitsis *et al*. These two groups used Florbetapir, as a biomarker for AD amyloid plaques, and [18F] T807 as the biomarker for CTE related tau protein (Dickstein et al, 2016, Mitsis et al, 2014). [18F] T807 was used specifically due to its preferential binding of tau protein as opposed to β-amyloid protein (Dickstein et al, 2016). Data regarding binding affinity shows a secondary benefit of biomarkers due to the observed protein binding preferences which further distinguishes between diseases. Radiopharmaceuticals have shown the ability to bind tau with such high specificity that it can target specific types of aberrant tau (Zimmer et al, 2014). Certain quinolone biomarkers such as THK-

PET Biomarkers			
Chemical derivative	*Biomarker*	*High affinity*	*Low affinity*
Naphthalene	*[18 F] FDDNP*	*Tau β-amyloid*	*TDP-43 aggregates α-synuclein*
Quinolone	*[18 F] THK-523*	*Tau*	*β-amyloid*
Quinolone	*[18 F] THK-5117*	*Tau*	*β-amyloid*
Quinolone	*[18 F] THK-5351*	*Tau*	*Non β-sheet conformations*
Benzimidazole Pyrimidines	*[18 F] T807*	*Tau*	*β-amyloid*
Benzimidizole Pyrimidines	*[18 F] T808*	*Tau*	*β-amyloid*
Benzothiazole	*[11 C] PBB3*	*Tau*	*Non β-sheet conformations*

Table 4. PET biomarkers suggested for identifying tau protein in the brain (adapted from Dani et al, 2016, Liu et al, 2007 and Zimmer et al, 2014).

5117 exhibit increased binding affinity for abnormal tau aggregates (Zimmer et al, 2014). Biomarkers also exhibit the ability to bind specific sites located with the aberrant tau (Zimmer et al, 2014).

b. <u>PET scanning in a living person</u>

Positron emission tomography can display uptake and spatial localization of low concentrations of radioactive biomarkers that have been intravenously administered (Gandy et al, 2014). [F-18] FDDNP, 2-(1- {6- [(2-[18F] fluoroethyl) (methyl) amino]-2-naphthyl} ethylidene) malononitrile, was developed as a PET biomarker for assessing neurodegenerative disease progression in a living person (Liu et al, 2007). Biomarkers exhibit high binding affinity for specific proteins involved in neurodegenerative diseases (Liu et al, 2007). Barrio and associates performed PET scanning on retired American football players who were deemed at risk of CTE development due to multiple concussive and sub-concussive events (Barrio et al, 2015). [F-18] FDDNP was used to image fibrillar neuroaggregates in the football players compared with a cognitively normal group and patients exhibiting Alzheimer's disease (Barrio et al, 2015). Topographical pattern formation determined in prior autopsy studies were also used when assessing PET scan patterns of fibrillar proteins (Barrio et al, 2015). The four stages of CTE development established by McKee *et al* (table 2) were used as parameters for identification of patterns for each stage of CTE development (Barrio et al, 2015). Patterns of tau in the brains of CTE suspected football players

exhibited similar results to prior determined autopsy results, and had a distinct difference from Alzheimer's patients (Barrio et al, 2015). Distribution volume ratios were used to assess differences in signal strength to indicate patterns which were used to establish stages of potential CTE development, and further distinguish suspected CTE from Alzheimer's disease in living participants (Figure 5) (Barrio et al, 2015). Suspected cases of CTE in a living person should be assessed by a PET scan since biomarker sensitivity is capable of identifying specific molecules (Gandy et al, 2014).

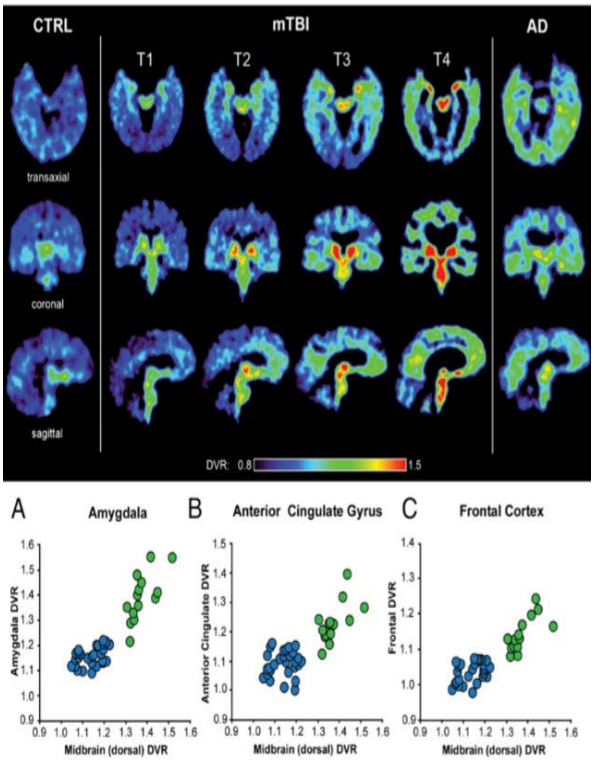

Figure 5. [F-18] FDDNP PET signal patterns for stages T1-T4, core regions were determined to be the amygdala and dorsal midbrain which consistently presented in the football player group indicated by stronger signals (Barrio et al, 2015). Overlap between brain locations found in Alzheimer's disease (AD) group and mTBI group were distinguished by a stronger signal in the mTBI grouping (Barrio et al, 2015).

3. DTI scanning

Diffusion tensor imaging (DTI) is a type of MRI that uses protons which are specifically found in water molecules as a noninvasive probe of neuroanatomy (Mori et al, 2006). DTI uses water flow along axons to determine anisotropic events, where water movement is parallel to axon fibers, and isotropic events where water moves perpendicular to axon fibers indicative of obstacles (Mori et al, 2006). One major benefit of DTI is fact that it can be performed in just a few minutes (Mori et al, 2006).

Studies involving use of DTI imaging for changes in neuroanatomy were constructed by Adam *et al* and Lipton *et al*. The soccer maneuver known as heading was found to display contrecoup injury with increased incidence of heading (Lipton

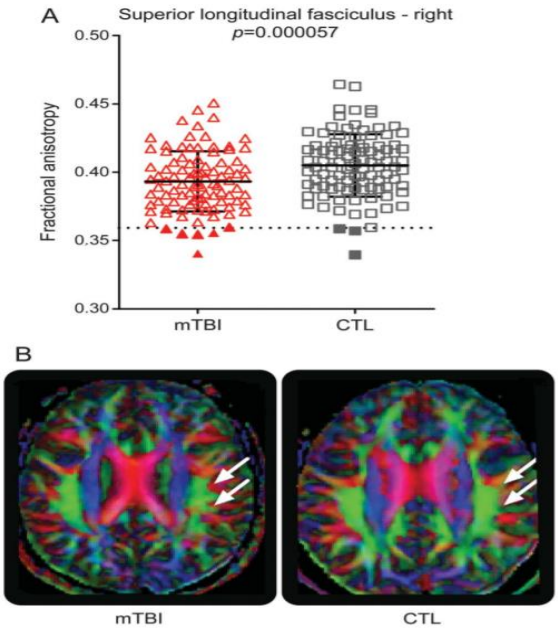

Figure 6. Part A displays the slight shift in fractional anisotropy values between mTBI groups of military personnel who experienced a blast-induced concussive event compared to normal uninjured controls (Adam et al, 2015). Part B displays DTI fractional anisotropy differences between a participant in the mTBI group and normal control with specific attention to the superior longitudinal fasciculus (Adam et al, 2015).

et al., 2013). DTI results identified three regions in the temporo-occipital white matter that had significantly low fractional anisotropy (FA) results (Lipton et al, 2013). Increased heading exposure was potentially correlated with lower FA results, however patient history did not explain these findings (Lipton et al, 2013). A study conducted in recently concussed military personnel using DTI imaging revealed slight changes in the FA results of the white matter of the brain as displayed in Figure 6 (Adam et al, 2015). Adam and associates reported that although the study was smaller, imaging resolution being substantially below quality and control participants were not perfectly matched, DTI was still able to relay some information regarding post concussive injury which could be beneficial for patient evaluations (Adam et al, 2015). Both studies displayed the benefit of having a noninvasive imaging procedure to examine patients (Adam et al, 2015, Lipton et al, 2013).

9. How imaging techniques will provide a more accurate diagnosis of CTE

Investigations of CTE development with compounded data from autopsy report and an imaging source, such as the one used in the Barrio *et al* study, are significantly useful for diagnosing the brain prior to death (Barrio et al, 2015). In epidemiological studies of CTE incidence evaluations of past autopsy report, imaging devices and clinical history have furthered the discussion regarding indirect risks associated with CTE development along with the known causation of repetitive mTBI (Mez et al, 2013). Research on biomarkers and imaging techniques furthers the discussion of CTE development and induces studies to continue on for this particular neurodegenerative disorder (Mez et al, 2013). Studies regarding CTE are suggested to involve a variety of scientific fields and resources in order to continue the discovery of new information pertaining to the disease (Gandy et al, 2014).

10. Potential treatments for CTE
    a. Lithium based treatment for mTBI

Lithium based treatment could be used as a preventative medicine against CTE development if administered to patients that present with a concussion (Leeds et al, 2014). Neuronal loss due to mTBI can spread out from the site of injury which is linked to glycogen synthase kinase-3 (GSK-3) activity (Leeds et al, 2014). GSK-3 exists in two different isoforms alpha and beta, however the beta isoform has been more strongly attributed to promoting apoptotic pathways following mTBI (Leeds et al, 2014). GSK-3 is one of the proteins responsible for normal tau phosphorylation at serine and threonine locations within a tau polypeptide (Lucke-Wold et al, 2014). Improper stimulation of this kinase protein leads to the hyperphosphorylation of tau and activation of apoptosis (Lucke-Wold et al, 2014). Lithium has the potential to inhibit the negative effects of GSK-3 through direct and indirect mechanisms (Jope, 2003, Leeds et al, 2014). Lithium acting directly on GSK-3 protein competitively inhibits magnesium ions from binding, which terminates further phosphorylation pathways (Jope, 2003, Leeds et al, 2014). Indirect inhibition of GSK-3 is thought to occur through phosphorylation of serine 9 (GSK-3β) or serine 21 (GSK-3α) by activated phosphatase proteins; the exact process by which this occurs is not fully understood (Leeds et al, 2014, Feng et al, 2014, Jope, 2003). Feng and associates showed that the neuroprotective qualities of lithium could be enhanced by compounding with valproate, another type of mood disorder drug with similar qualities to lithium (Feng et al, 2014, Leeds et al, 2014). Individuals hospitalized for mTBI could benefit acutely from the effects of lithium based treatments. CTE could be deterred by inhibiting hyperphosphorylated tau development in the initial stages of injury.

IV. Past and current opinions on CTE in sports
    1. Societal views
        a. Acceptance of facts

Extensive coverage of CTE in the media is thought to be the reason why many athletes, especially football players, are volunteering for studies regarding disease related changes (Seichepine et al, 2013). The NFL's response to increased concussion awareness has resulted in frequent policy changes, however the reasoning behind the rule changes

could be to avoid litigation (Anderson et al, 2012). Current concussion guidelines should prevent players from returning to play if a concussion is suspected (Anderson et al, 2012). Michael Strahan a retired football player, related that athletes should be protected from themselves when it comes to handling players with concussions (FOX Sports, 2009). Jimmy Johnson, a former NFL coach, shared that if a player had a concussion the player would not be returned to game play without approval by the NFL team medical staff (FOX Sports, 2009). The sentiments of Johnson and Strahan gives a small indication that the attitude towards protecting concussed individuals from further play are encouraged (FOX Sports, 2009).

The NFL has begun working together with NIH researchers by acting as financial support to further conduct research in the areas of mTBI and CTE (Gandy et al, 2014). Jeff Miller, the top health and safety officer of the NFL, positively affirmed that CTE is a real risk for football players during a discussion with the U.S. House of Representatives Committee on Energy and Commerce which featured concussions as a topic (Fainaru, ESPN article, 2016). Wider media coverage about the potential link between multiple concussions and CTE has triggered a discussion in the athletic community. Information gathered from research on CTE can further help coaches, players and the sports community to truly understand the dangers of concussions.

b. Denial of facts

Despite the evidence of a potential link between CTE and multiple concussions the formulation of a plan to help protect players has been underwhelming. It appears that major sports corporations, involved with rule decision making and player protection, are less inclined to make changes that would affect their profitability (Goldberg, 2013). Furthermore, past actions of NFL coaches and side-line medical staff has led to a lack of response to player care to prevent a player from returning to play with a concussion (Goldberg, 2013). Prior to the admission of CTE related risk by Miller, the NFL strongly denied any evidence of potential dangers to players posed by game play (Gandy et al, 2014, Fainaru, 2016). Football players, like Ray Lewis and Terry Bradshaw, have

extremely negative views on how the NFL views the athletes (Fox Sports, 2009, Charlie Rose, 2015). Terry Bradshaw made it clear that the reasoning why there has been a lack of response from the NFL has been due to greed and a complete lack of care (Fox Sports, 2009). Ray Lewis expressed that the NFL does not care about players and that that is the reason why athletes are the only individuals that are penalized (Charlie Rose, 2015). Lewis further puts the NFL in a poor light by advocating that concussions are not a danger, but merely a part of the job (Charlie Rose, 2015).

One potential area for investigation in the problem with concussed players remaining in play would be with the team specific medical staff and interactions with coaches. In an anonymous web survey submitted to NCAA athletic trainers and clinicians for college level sports, over half of the participants responded positively to experiencing pressures from coaches (64.4%) and athletes (53.7%) to return concussed players earlier than advised to game play (Kroshus et al, 2015). Sex and years of experience also played a role in how coaches and athletes treated clinical staff; females and clinicians with fewer years of experience were more likely to be pressured by coaches or athletes (Kroshus et al, 2015). One primary reason suggested for pressure on clinicians and trainers to return injured athletes to play was based on which NCAA division category the personnel provided care (Kroshus et al, 2015). While the number of participants may have been lower than expected the results show a benefit to collecting data anonymously (Kroshus et al, 2015).

Athletes are another group of interest when evaluating the problems regarding concussion awareness and reporting concussive injuries. In a recent telephone survey 472 athletes, of various sports and levels of sport, were asked about previous concussive history in comparison to an older definition and an updated definition of concussion (Robbins et al, 2014). Sports included in this study were diverse including both full-contact sports and non-contact sports which broadened the definition of athletic types where concussions could be a risk (Robbins et al, 2014). Participants voluntarily responding to the study showed an increase in the number of perceived injuries after

being told the updated definition of what is considered a concussion (Robbins et al, 2014). Current and retired athletes responding to the study seemed to be more aware of the outdated definition of a concussion, however this was attributed to the time at which the athlete performed the sport (Robbins et al, 2014). Robbins *et al* proposed that clinicians should inform athletes earlier in the season as to what counts as a concussion (Robbins et al, 2014). Negative involvement of clinicians in concussive care and an apparent lack of information on concussions from this group shows a further demand for investigation on the level of involvement clinicians have with athletes (Kroshus et al, 2015, Robbins et al, 2015. It is clear that once given a current definition of a concussion that athletes become better educated, which could lead to more accurate reporting of concussive events (Robbins et al, 2014).

2. Athlete complaints

a. Litigation

Amidst the awareness of CTE and its link to repetitive mTBI athletes that participated in full-contact sports have sought compensation via legal action. Case history regarding these claims are limited due to the fact that many cases are quickly ushered into settlement agreements. In a particular case against the NFL, retired football players were required to enter into settlement agreements due to rules created by the NFL which were presented at the time of contract signing (In re National Football League Players, 2015). Claims brought against the NFL were related to a lack of information regarding concussions and the potential for further harm stemming from these injuries (In re National Football League Players, 2015). Retired football players further added that the promotion of aggressive behaviors by the NFL also lead to player endangerment (In re National Football League Players, 2015). Negotiations between the two parties were extensive and prior to the judicial intervention the NFL had created another suspiciously worded agreement (In re National Football League Players, 2015). In regards to CTE, a diagnosis is only confirmable by autopsy report and therefore money awarded for developing the disease is only granted after an athlete's death; this is in the sum of $4 million dollars (In re National Football League Players, 2015). Proof of negligence by the NFL, as an employer, is evident and the fact that 20,000 NFL athletes were

involved in the settlement displays that athletes feel mislead and mistreated by the individuals in charge of player safety and guideline regulations (In re National Football League Players, 2015).

Six retired National Hockey League (NHL) players entered into litigation with the NHL over the same claims as the retired NFL players (In re National Football League Players, 2015, In re National Hockey League Players, 2016). One, albeit morbid, benefit that is helping hockey players display negligent actions of the NHL was the decision to require players to wear helmets which occurred in the late 70's (In re National Hockey League Players, 2016). While the NHL argues that players should have understood risks of injury at the time of contract signing, and that this does not require the NHL to have significant involvement in player protection (In re National Hockey League Players, 2016). Retired players also cited that in the late 90's protective shielding around the hockey rink was required to be more flexible to prevent injuries to athletes (In re National Hockey League Players, 2016). Promotion of violence in the sport was also cited against the NHL, however the NHL did not agree with this claim and argued that rules created should be examined to determine if the NHL has the ability to enforce them (In re National Hockey League Players, 2016).

Retired athletes from two different full-contact sports presented similar claims against former employers on their own behalf as well as, on the behalf of all other players (In re National Football League Players, 2015, In re National Hockey League Players, 2016). Retired NHL players admitted that experiencing hits from other players was within the scope of employment, however long-term effects to the brain did not fit into perceived risks upon contract signing (In re National Hockey League Players, 2016). In both cases retired athletes felt mislead and poorly educated about potential risks and that current information regarding neurodegenerative diseases, like CTE, have prompted the request to enter into litigation (In re National Football League Players, 2015, In re National Hockey League Players, 2016).

b. Quality of life with CTE

Jim McMahon, a former NFL player, along with other NFL retirees discussed the suicide of Dave Duerson in an interview on ESPN (Youtube, CTE, 2016). The NFL retirees went on to discuss Duerson's complaints regarding memory problems, headaches and feelings of aggression (Youtube, CTE, 2016). McMahon sought medical treatment after experiencing similar cognitive and emotional problems to Duerson (Youtube, CTE, 2016). Jim McMahon was diagnosed with early-onset dementia which stemmed from a severe decrease in cerebrospinal fluid flow just below the skull (Youtube, CTE, 2016). Damage to McMahon's brain is irreversible but early diagnosis has helped McMahon develop a regiment to deal with memory loss and pain (Youtube, CTE, 2016). Dave Duerson's suicide has been taken very seriously by former players of the NFL and many expressed deep concerns of developing similar issues (Youtube, CTE, 2016).

Former mixed martial arts athlete Gary Goodridge spoke bluntly about what life is like with neurodegenerative dementia (Youtube, AXS TV Fights, 2016). Goodridge made similar complaints to other athletes suffering from CTE type symptoms citing aggression, memory problems, suicidal thoughts and occasional slurred speech (Youtube, AXS TV Fights, 2016). Early detection and medicinal intervention is what Goodridge attributes to aiding everyday life (Youtube, AXS TV Fights, 2016). In a video diary of Goodridge's daily activities there were frequent complaints of feeling tired, argumentative and confusion or forgetfulness (Youtube, AXS TV Fights, 2016). In terms of a long-term prognosis for Goodridge's mental state, it is expected that cognitive decline will continue until death (Youtube, AXS TV Fights, 2016).

Research by Omalu *et al* and McKee *et al* presented findings of cognitive and behavioral changes in athletes suspected of having CTE. In a case presented by Dr. Bennet Omalu *et al* the first indication of CTE as a result of football related concussions were displayed (Omalu et al, 2005). Patient history collected from surviving relatives showed the NFL player experienced changes in behaviors, issues with executive function and Parkinson's type symptoms, although it was noted that no Lewy bodies were present

at time of autopsy (Omalu et al, 2005). McKee and associates highlighted specific cases of players, one football player and two boxers (McKee et al, 2009). In one case an American football player experienced a decrease in memory, and aggression which continued to worsen until death from an accidental gunshot wound (McKee et el, 2009). Patient histories for the two boxers revealed behavioral changes, especially extremely aggressive behavior which often lead to abusive actions against family members, and severe memory loss (McKee et al, 2009). Findings presented by researchers, retired athletes and surviving family members depict a poorer quality of life as an expected outcome for athletes that have suffered multiple blows to the head.

V. Potential solutions for prevention of CTE

1. Updating equipment (currently in testing stage)

a. Shock absorbing helmets (VICIS Zero 1 helmet)

A group of engineers and neurosurgeons in Washington state began working together to create VICIS which implements protective technology into helmets for football (VICIS Co., 2016). VICIS associates have engineered a helmet that is comprised of two layers with compressing filaments that respond to external force by twisting and bending in various directions (Patent 20160255900 A1, 2014). Potential for accelerometer sensors to be built into the helmet via the filaments to relay information regarding components of forces to a coach or database for further research has been proposed (Patent 20160255900 A1, 2014). VICIS also offers a custom fitting for each helmet purchased so that the equipment is player specific (VICIS Co., 2016). While the company does not suggest that the helmet will prevent concussions completely, it is suggested that this equipment upgrade will provide more protection than current helmets (VICIS Co., 2016).

2. Side line test and return-to-play instructions

An underlying theme observed when evaluating research regarding concussion reporting showed that athletes tend to report less symptoms and concussions than actually experienced (Kroshus et al, 2014, Williams et al, 2015). 47.83% of division III hockey players responded to having experienced concussive symptoms but did not report

(Kroshus et al, 2014). One suggested reason for these omissions seems to stem from player's perception of whether the team's personnel (i.e. coaches, medical staff, athletic trainers) would be understanding to the presentation of concussion symptoms (Kroshus et al, 2014). Another reason involves player's perceptions on how taking time to recover will negatively impact a position in the game or whether the coach will allow that player back into the game (Kroshus et al, 2014, Williams et al, 2015). Education on how an injured player who does not report would create unnecessary problems for the team if a concussion went unreported was a proposed incentive for reporting concussions and concussion symptoms to coaches and medical staff (Kroshus et al, 2014). Opening dialogue between coaches and athletes on returning to play rules was suggested as an option for alleviating players concerns regarding participation (Kroshus et al, 2014). Overall, it was advised that player and coach education regarding concussions and reporting should help with solving the concussion reporting problem (Kroshus et al, 2014).

Determination of an athlete's recovery relies solely on the symptoms reported and the length at which the symptoms were experienced (Williams et al, 2015). Williams and associates determined from studies of high school and college level athletes that recovery time for concussion symptoms were not the same between the two groups; high schoolers reported recovering in 15 days versus the 6 days to recover for college athletes (Williams et al, 2015). Cognitive recovery times varied slightly between the two groups but were counted as similar findings, high school athletes within one week and college athletes recovered within 5 days (Williams et al, 2015). Establishing a timeline for concussion symptoms would be beneficial for players and coaches to deter further brain injury during recovery (Williams et al, 2015). Williams *et al* suggested that variability between concussive symptoms shows that players would benefit from individualized care for recovery (Williams et al, 2015). However, since concussions can be difficult to diagnose it was suggested that return-to-play guidelines should be followed for an athlete's recovery (Williams et al, 2015).

Athletic trainers and medical staff for full-contact sports experience difficulties in making a true concussive assessment when relying on players reported symptoms (Williams et al, 2015). In some cases, medically trained staff may not be present due to the level at which the sport is played (Leong et al, 2014). In light of the need for a quick and uncomplicated concussion assessment tool, the King-Devick sideline test was created (Leong et al, 2014). Concussions are determined by evaluating an athlete's verbal and visual response to reading numbers depicted on cards in a short amount of time (Leong et al, 2014). Administration of this test to athletes revealed that concussed players experienced an increase in time needed to complete the test compared to uninjured players (Leong et al, 2014). King-Devick test results were compared to standard tests for concussion evaluation (Leong et al, 2014). College football players suspected of concussion were given all tests and the majority, with one player exception, could not pass the tests administered (Leong et al, 2014). Early detection of concussion using the King-Devick test was proposed as a quick method to successfully remove injured players from a game (Leong et al, 2014).

3. Putting an age limit on certain full-contact sports

It is difficult to determine how CTE development is propagated in younger brains as a result of mTBI (Turner et al, 2015). McKee and associates propose that the development of hyperphosphorylated tau and trauma are linked, but that many variables are involved in CTE development including the age at which trauma has occurred (McKee et al, 2015). While symptoms of CTE usually take years to present clinically, confirmation of symptoms have been found in individuals as young as 14 years of age (Mez et al, 2013). Individuals suffering from CTE related symptoms compose an older demographic which could be attributed to poor equipment standards of the past (Omalu et al, 2005). Explanation of risks associated with full-contact sports may help formulate a range of ages individuals may choose to participate in these sports (Gandy et al, 2014.)

4. Avoidance of full-contact sports

Despite direct advisory from medical organizations and public opposition to excessively violent full-contact sports, these athletic events continue to thrive (Gandy et al, 2014). In current research, there has been a lack of a straight forward opinion on whether full-contact sports propose significant enough risk to warrant the banning of full-contact sports. Lipton *et al* recommended that soccer players may need to be limited in the number of times that athletes head the ball due to a discovery between heading events and structural changes to the temporo-occipital white matter of the brain (Lipton et al, 2013). McKee *et al* and Omalu *et al* both suggest that despite findings of CTE in the brains of former athletes the evidence presented cannot formulate a direct relationship between full-contact sports and CTE (McKee et al, 2013, Omalu et al, 2005).

VI. Personal opinion

Establishing a solid link between head trauma and CTE is still in an early stage of development. McKee and associates have built a strong model for disease development that will effectively help identify tau formation in the brain when compared to imaging techniques. However, the exact cause of CTE is most likely multifactorial in nature. Biomarker and scanning techniques will be critical tools for living patients suspected of having CTE, and how the disease develops over time. Research from this review revealed that there are multiple areas where questions could arise and how these topics relate to disease development. Imaging techniques will provide valuable information on many of the areas where questions remain. My personal opinion regarding concussions and long term risks of potential CTE development is that there must be a link between mTBI and disease development within the brain. Time and further research will develop better answers regarding the full picture of disease causation and development. However, health risks arising from head trauma does not seem to be beyond the scope for causing serious problems in the future.

1. Questions for further research
   a. What areas should receive further research?

Topics where data are unclear regarding relationships varies from the activity that was responsible for initiation of the disease to protein processes and

genetics. Age and the role it plays in disease development is one area of interest due to a lack of data regarding biological processes in the aged. Questions regarding the differences between the effects of concussive damage in younger and older individuals are especially important. If it was established that head trauma at an earlier age effects proper brain development in children and adolescents, there would need to be changes made to age limits for full-contact sports.

Gender and the role that hormones play in disease development are also warranted. In this review it was clear that the potential for females to be better protected by hormonal processes could explain why the number of reports of CTE type symptoms are predominantly in males. However, it should be noted that female brains and data regarding female full-contact athletes is sparse if available at all.

Certain predisposing genotypes such as the APOE phenotypes and how that could lead to CTE development is also an area where further research should continue. One glaring factor that makes establishing a cause and effect relationship difficult is the variability between patients. In general, human beings do not all function the same way and the addition of the factors above add to the difficulty of establishing clear data. However, further research in these areas will not only benefit studies regarding CTE but will also generate pertinent data for the neurodegenerative disease research community, as well as many others.

Research should continue to spread to areas beyond a laboratory setting. Data are missing from areas regarding concussion potential from non-contact sports and every type of full-contact sport that could be involved. Types of injuries should be evaluated on which impacts could present more harm than others and what forces are needed to generate the most damage. Sports

equipment should also undergo serious stress testing to determine where faults may lie and how those defects can be prevented.

b. Should full-contact sports be banned?

Full-contact sports are a large part of American culture. Michigan residents in particular have a strong devotion to football and ice-hockey. Increased news regarding athlete suicides and the expressed concerns of surviving retired players are startling. Clearly there is a need for answer to this health concern. Promotion of violence in full-contact sports has significantly skewed what my perceived goals of sports used to entail. Younger individuals are being pushed into acting with excessive violence against other young athletes for the sake of winning a trophy, or a title. I do not believe that this makes any sort of sense, and I worry for those that believe sacrificing the brains of athletes is worth attaining some award. Placing the blame on who is directly responsible for allowing this to happen is difficult to determine, whether it was the fault of coaches or larger groups like the NFL requires some clarity. There are a variety of other sports that athletes could continue to thrive in where risks of concussion are virtually nonexistent. It would be in the best interest of athletes to investigate these other potential sports options because the overall risk of CTE development is not worth developing this disease.

2. Pros and cons of current research
   a. Low coverage for all age ranges and sexes

Age as a factor in CTE development was very imbalanced when I observed the current research. Many of the research participants were middle-aged or older. In certain cases, older (i.e. 65+) individuals presented with comorbid diseases making it difficult to identify which disease was involved with a patient's symptoms. If the data were not clear, then removing that information was necessary. Removal of confounding data decreases the sample size and detracts from the value of the study. Biomarker use in surviving individuals will help in distinguishing between diseases that are developing.

Data regarding potential CTE development in females is extremely low. Since football has gained the most attention for potential CTE risk it is not surprising that female athletes have been over looked during research. It would be of benefit to investigate whether CTE develops in the brains of female athletes in the same manner as it does in males. One of the reasons I chose to cover estrogen as a protective hormone was due to the lack of data. If hormones play a larger role in CTE research, this could lead to further breakthroughs in finding cures to prevent the spread of this disease. While selection bias has been a concern throughout the study of CTE adding female full-contact sport athletes to the study populations would alleviate a part of that problem.

b. Sample sizes and types of studies

Sample sizes tended to be rather small in the earlier years of CTE research but have started to grow as athletes learn more about the disease. Full-contact sport athletes have a desire to know what might happen in the future and how to prepare if diagnosed with CTE. In general, larger and more diverse sample sizes should be included in CTE research.

One aspect to consider when conducting CTE research is including anonymity. Certain groups may feel more secure if the data does not easily distinguish specific individuals from others. Anonymous responders may also have pertinent information regarding areas of sports medicine that need further investigation. It was a benefit in the study conducted by Kroshus *et al* and will most likely help improve ethical standards for medical and sport related staff.

A consistent theme observed in my research was the need for longitudinal studies. Research observed relied heavily on cross-sectional studies, qualitative studies and meta-analysis to establish connections between CTE and head trauma. Qualitative studies have a slight benefit by providing descriptions of sports where concussions are of a greater risk. However, the impact data required to cause a concussion seems far more important in understanding

disease development. I believe that use of imaging and biomarkers will be beneficial for studies that are attempting to track the disease properly for longitudinal data to be collected.

VII. Conclusion

CTE research is ongoing and is attempting to answer many of the questions that have arose during studies, or that appear to be related to the disease. The findings of McKee *et al* have established a significant model for use in imaging techniques for comparing images to autopsy reports (Barrio et al, 2015, McKee et al, 2013). Research in a variety of associated sciences should continue to collaborate as studies regarding CTE development continue (Gandy et al, 2014).

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